Current Role of PCSK9 Inhibitors

Vera Bittner, MD, MSPH, FACC
Professor of Medicine
Section Head, General Cardiology, Prevention, and Imaging
Medical Director, Coronary Care Unit and Cardiac Rehabilitation
University of Alabama at Birmingham
**Proprotein Convertase Subtilisin-Kexin Type 9**

- Secreted serine protease
- Targets the LDL-receptor for degradation
  - May also influence Apo B synthesis and TG secretion
- Gain of function mutation → higher LDL-C
- Loss of function mutation → lower LDL-C

### FDA Approval August 2015

<table>
<thead>
<tr>
<th>Alirocumab (Praluent)</th>
<th>Evolocumab (Repatha)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adjunct to diet and maximally tolerated statin to treat adults with HeFH or clinical ASCVD who need more LDL-C reduction</strong></td>
<td><strong>Adjunct to diet and maximally tolerated statin to treat adults with HeFH or clinical ASCVD who need more LDL-C reduction</strong></td>
</tr>
<tr>
<td><strong>Adjunct to diet and other LDL-lowering Rx (e.g., statins, ezetimibe, LDL apheresis) in patients with HoFH who need more LDL-C reduction</strong></td>
<td><strong>Adjunct to diet and other LDL-lowering Rx (e.g., statins, ezetimibe, LDL apheresis) in patients with HoFH who need more LDL-C reduction</strong></td>
</tr>
</tbody>
</table>

### Alirocumab Dose
- Initiate 75 mg SQ every 2 weeks
- May ↑ dose to 150 mg every 2 weeks

### Evolocumab Dose
- **ASCVD or HeFH**
  - 140 mg SQ every 2 weeks or 420 mg SQ monthly
- **HoFH**
  - 420 mg SQ monthly
LDL-C Effects on Statin Background

ODYSSEY Longterm

Alirocumab

Evolocumab

Sabatine et al. NEJM 2015;372:1500-9
Robinson et al. NEJM 2015;372:1489-99
Heterogeneity of Response to PCSK9 Inhibition

- Pooled data from 10 trials in the Phase 3 ODYSSEY Program
- Treatment for 24-104 weeks
- 52% of alirocumab treated individuals achieved LDL-C <50 mg/dL in placebo-controlled studies

Post-hoc Data on CV Outcomes

Robinson et al. NEJM 2015;372:1489-99
Sabatine et al. NEJM 2015;372:1500-9

ODYSSEY Longterm (Alirocumab)
HR = 0.52 (95% CI 0.31-0.90)

OSLER (Evolocumab)
HR 0.47 (95% CI 0.28-0.78)
FOURIER Trial

- N=27,564
  - ASCVD
  - LDL-C ≥ 70 mg/dL* on statin therapy
- Median F/U 2.2 years
- Evolocumab vs placebo
- LDL-C reduction 59% (90 --> 30 mg/dL)

1° EP: CV death, MI, stroke, hospitalization for UA, or coronary revascularization

2° EP: CV death, MI, or stroke

*1.8 mmol/L

Sabatine et al. NEJM 2017;376:1713-1722
## FOURIER Adverse Events

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Evolocumab (N=13,769)</th>
<th>Placebo (N=13,756)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>10,664 (77.4)</td>
<td>10,644 (77.4)</td>
</tr>
<tr>
<td>Serious</td>
<td>3410 (24.8)</td>
<td>3404 (24.7)</td>
</tr>
<tr>
<td>Thought to be related to the study agent and leading to discontinuation of study regimen</td>
<td>226 (1.6)</td>
<td>201 (1.5)</td>
</tr>
<tr>
<td>Injection-site reaction*</td>
<td>296 (2.1)</td>
<td>219 (1.6)</td>
</tr>
<tr>
<td>Allergic reaction</td>
<td>420 (3.1)</td>
<td>393 (2.9)</td>
</tr>
<tr>
<td>Muscle-related event</td>
<td>682 (5.0)</td>
<td>656 (4.8)</td>
</tr>
<tr>
<td>Rhabdomyolysis</td>
<td>8 (0.1)</td>
<td>11 (0.1)</td>
</tr>
<tr>
<td>Cataract</td>
<td>228 (1.7)</td>
<td>242 (1.8)</td>
</tr>
<tr>
<td>Adjudicated case of new-onset diabetes†</td>
<td>677 (8.1)</td>
<td>644 (7.7)</td>
</tr>
<tr>
<td>Neurocognitive event</td>
<td>217 (1.6)</td>
<td>202 (1.5)</td>
</tr>
</tbody>
</table>

Sabatine et al. NEJM 2017;376:1713-1722
Cost

Listed price in US: ≈ $14,000 / year

Primary Endpoint
• Absolute RR 1.5% $\rightarrow$ NNT 74 (for 2 years)
• Cost for 2 years of treatment to prevent 1 event: $2,072,000

Secondary Endpoint
• Absolute RR 1.3% $\rightarrow$ NNT 77 (for 2 years)
• Cost for 2 years of treatment to prevent 1 event: $2,156,000

Sabatine et al. NEJM 2017;376:1713-1722
Applying FOURIER to the VA Population

Cost in US Dollar

- Evo for all FOURIER eligible patients
- Cost of statin titration and addition of ezetimibe
- Evo for those with LDL-C 70 mg/dl or greater
- Statin/ezetimibe titration plus selective Evo

Virani et al. Circulation 2017, May; Epub ahead of print
Take Home Points

• PCSK9 Inhibitors are powerful LDL-C lowering agents.
  • Response to PCSK9-inhibition is heterogeneous

• Evolocumab reduced events in the FOURIER trial and there was no major safety signal
  • Event reduction less robust than estimated from the pooled post-hoc analyses
  • Follow-up was very short

• PCSK9 inhibitors are expensive
  • Intensification of statin and addition of ezetimibe can reduce the need for PCSK9 inhibition and significantly reduce costs
Muchas gracias por su atención!